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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SERGEY A. LUKYANOV,
ARCADY F. FRADKOV, YULII A. LABAS,
MIKHAIL V. MATZ, and ALEXEY TERSKIKH[1]

Appeal 2015-007204
Application 11/607,828
Technology Center 1600

Before CHRISTOPHER G. PAULRAJ, TAWEN CHANG, and
RYAN H. FLAX, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to certain nucleic acids, nucleic acid constructs, and expression cassettes, which have been rejected as lacking in written description and/or as directed to patent ineligible subject matter. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm in part.

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[1] Appellants identify the Real Party in Interest as Clontech Laboratories, Inc. (Appeal Br. 3.)

STATEMENT OF THE CASE

According to the Specification, "[l]abeling is a tool for marking a protein, cell, or organism of interest and plays a prominent role in many biochemistry, molecular biology and medical diagnostic applications. . . . Of particular interest is the development of new protein labels, including chromo- and/or fluorescent protein labels." (Spec. 1:30–2:2.) Further according to the Specification, the present invention relates to "proteins that are colored and/or fluorescent, where this feature arises from the interaction of two or more residues of the protein," as well as the nucleic acids encoding these proteins. (*Id.* at 2:20–23.) The Specification states that the proteins of the invention are "either obtained from non-bioluminescent Cnidarian, e.g., Anthozoan, species or . . . Anthozoan non-Pennatulacean (sea pen) species." (*Id.* at 2:23–26.)

Claims 71–107 and 109–115 are on appeal. Claim 71 is illustrative and reproduced below:

> 71. A nucleic acid construct, the construct comprising:
> a vector; and
> a continuous open reading frame coding sequence that encodes a nonbioluminescent Anthozoan chromo- or fluorescent polypeptide or chromo- or fluorescent mutant thereof, wherein the polypeptide or mutant thereof has an average molecular weight of 17.5 to 32.5 kDa, comprises a β-can fold and a chromophore or fluorophore, and has an absorbance maximum in the range of 300–700 nm and an emission maximum in the range of 400–800 nm.

(Appeal Br. 119 (Claims App'x).)

The Examiner rejects claims 71–107 and 109–115 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. (Ans. 4.)

The Examiner rejects claims 71–74, 76–82, 88, 91, 93, 95, 97, 99, 103, 109–111 and 114 under 35 U.S.C. § 101 as directed to patent ineligible subject matter. (Ans. 9.)

I.

Issue

The Examiner has rejected claims 71–107 and 109–115 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement.

The Examiner finds that claim 71 can be construed as "any nucleic acid that encodes any [non-bioluminescent Anthozoan] chromo or fluorescent protein or a mutant thereof, wherein the polypeptide has three characteristics (β-can fold, average molecular weight of 17.5–32.5kDa and a chromophore/fluorophore)." (Ans. 5, 7.) The Examiner finds that claim 71 and similar claims (e.g., claims 85 and 88), are "overly broad and encompass a genus of structures not adequately described," and that the Specification "fails to provide a representative number of species for the claimed genus to show that applicant was in possession of the claimed genus." (*Id.* at 5–6, 7.)

In particular, the Examiner finds that "[t]he recited molecular weight is not accompanied by a specific method used to derive[] said molecular weight" and that, in any event, molecular weight does not sufficiently define the protein recited in the claim. (*Id.* at 5.) The Examiner finds that the recited β-can fold and absorbance information also do not provide structural information sufficient to satisfy the written description requirement. (*Id.* at 6.) The Examiner further finds that the dependent claims that recite reference polypeptide sequences, such as claims 72 and 109–115,

nevertheless fail to satisfy the written description requirement. (*Id.*) The Examiner argues that these claims still encompass "an enormous amount of variability," because they claim sequences with just at least 40% or 70% identity to the reference sequences. (*Id.*)

Likewise, with respect to dependent claims reciting specific types and species of mutation (e.g., claims 89 and 90), the Examiner finds the claims lack written description because the claims do not sufficiently identify the claimed sequence(s) that contain the recited mutation(s) so as to correlate structure and function. (*Id.* at 7.) With respect to claims 104 and 105, the Examiner finds that the Specification additionally lacks description of the recited "humanized" nucleic acid. (*Id.* at 8.) With respect to claims 106 and 107, the Examiner finds that the Specification further does not sufficiently describe the "large genus of [recited] nucleic acid primers of 15 to 100 nucleotides that could hybridize under stringent conditions to a nucleic acid or the complement thereof" that encodes a polypeptide recited in the claims. (*Id.* at 6–7.)

Appellants contend that claim 71 recites six characteristics of peptides encoded by the claimed genus of nucleic acid, including the structural characteristics of (1) molecular weight, (2) a β-can fold, and (3) the presence of a chromophore/fluorophore, as well as the functional characteristics of (4) color/fluorescence, (5) absorbance maximum, and (6) emission maximum.

(Appeal Br. 19.) Citing Yang,[2] Ormö,[3] Lehninger,[4] and Friedberg,[5] Appellants contend that these characteristics in combination "provide a sufficient number of properties of the polypeptides encoded by the claimed nucleic acids to describe the claimed genus of nucleic acids sufficiently so as to demonstrate that Appellants are in possession of the pending claimed genus." (*Id.* at 20.)

Appellants further contend that the Specification discloses "48 examples of continuous open reading frame coding sequences encompassed by the pending claimed genus of nucleic acid constructs," including 9 wild-type nucleic acid sequences obtained from 8 different wild-type Anthozoan species as well as 39 mutant nucleic acid sequences. (*Id.* at 20–21, 23.) Citing Daly[6] and the McFadden Declaration,[7] Appellants argue that these exemplary sequences provide "a representative number of species of continuous open reading frame nucleic acids encompassed by the pending

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[2] Fan Yang et al., *The Molecular Structure of Green Fluorescent Protein*, 14 NATURE BIOTECHNOLOGY 1246 (1996).
[3] Mats Ormö et al., *Crystal Structure of the* Aequorea victoria *Green Fluorescent Protein*, 273 SCIENCE 1392 (1996).
[4] 1 Albert L. Lehninger et al., *Principles of Biochemistry* 87 (4th ed. 2005). We note that no copy of Lehninger was provided in the record.
[5] Iddo Friedberg & Hanah Margalit, *Persistently Conserved Positions in Structurally Similar, Sequence Dissimilar Proteins: Roles in Preserving Protein Fold and Function*, 11 PROTEIN SCIENCE 350 (2002).
[6] Mary Megan Daly et al., *The Phylum Cnidaria: A Review of Phylogenetic Patterns and Diversity 300 Years After Linnaeus*, 1668 ZOOTAXA 127 (2007).
[7] Declaration of Catherine McFadden, Ph.D. under 37 C.F.R. § 1.132 (Mar. 30, 2010).

claims." (*Id.* at 22–24.)

With respect to claim 72 and other claims reciting reference polypeptide sequences, Appellants argue that, in light of the disclosure of the reference sequences, the teaching in the Specification of "homologs [that] may have at least about 40% sequence identity with the disclosed fluorescent polypeptides," and the fact that certain of the reference polypeptide sequences are highly conserved, a skilled artisan would reasonably conclude that the inventors had possession of the claimed inventions. (*See, e.g., id.* at 28–29, 31, 32–33, 34–35, 44, 46, 47–52.)

With respect to claims 104 and 105, which contain a limitation relating to humanized nucleic acid, Appellants argue that it is well known in the art that "humanization of nucleic acids involves the creation of a synthetic nucleic acid through the replacement of endogenous codons with human preferred codons coding for the same amino acid as the endogenous codon." (*Id.* at 45.) Appellants argue that, given the "well-understood nature of the humanization of nucleic acids within the art of molecular biology" and the specific examples of humanized nucleic acids encoding for fluorescent proteins, the Specification has sufficiently described the limitation. (*Id.*)

With respect to claims 106 and 107, which contain limitations relating to certain nucleic acid primers, Appellants argue that "[t]he [S]pecification describes small DNA fragments of the subject nucleic acids [to be] useful as PCR primers" and that use of such primers is well-understood in the art. (*Id.* at 47.) Accordingly, Appellants argue that the Specification satisfies the written description requirements with respect to these limitations. (*Id.*)

The issue with respect to this rejection is whether the evidence of

record supports the Examiner's conclusion that claims 71–107 and 109–115 fail to comply with the written description requirement.

Analysis

Claim 71

Regarding claim 71, we find Appellants to have the better argument. Claim 71 is directed to a nucleic acid construct comprising a vector and a continuous open reading frame coding sequence encoding a wild type or mutant Anthozoan polypeptide defined by the following properties: (1) it is a chromo- or fluorescent polypeptide; (2) it has an average molecular weight of 17.5 to 32.5 kDa; it comprises (3) a β-can fold and (4) a chromophore or fluorophore; (5) it has an absorbance maximum in the range of 300–700 nm; and (6) it has an emission maximum in the range of 400–800 nm.

The Federal Circuit has stated that

> [t]he written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics … i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics."

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir. 2002) (citation omitted). Furthermore, description of a genus is sufficient where there is "disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (citation omitted).

In this case, we find that the evidence submitted by Appellants

satisfies many of the factors cited by *Enzo* and *Ariad* for the written description requirement. The Specification discloses a structural feature common to the polypeptides encoded by the claimed nucleotide sequence, i.e., the β-can fold with a chromophore or fluorophore, which is known to correlate with the claimed functional characteristics of color / fluorescence. (*See generally* Yang and Ormo.) The Specification also provides the amino acid sequences of the encoded polypeptides from eight Anthozoan species and the corresponding cDNA sequences, including an alignment of the amino acid sequences of these polypeptides showing specific amino acids that are conserved across the species. (Spec. Figs. 1–9, 23, Table 1.) The Specification further describes different amino acid changes that can be made in the wild-type sequences without eliminating the protein's color and/or fluorescence. (*See, e.g.*, Spec. Table 2.) Finally, Appellants have submitted an expert declaration from Dr. Catherine McFadden stating that the eight Anthozoan species discussed in the Specification are representative both of "the two subclasses that make up the Class Anthozoa" and of "the diversity of polyps between and within these two subclasses." (McFadden Decl. ¶¶ 10–12.) Dr. McFadden further opines that, "in view of the number and diversity of nonbioluminescent Anthozoans identified by [Appellants] as organisms that expressed fluorescent proteins," a skilled artisan would reasonably expect that the fluorescent proteins recited in the claims "were conserved in species across the Class Anthozoa." (*Id.* at ¶¶ 9–13.)

The Examiner finds the above disclosure and evidence lacking because "[n]o specific nucleotide sequence with a corresponding expression product is claimed" in claim 71. (Ans. 15–16.) There is no requirement, however, that a ***claim*** must recite a reference sequence in order to satisfy

written description. *Cf. Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005) (holding that even specifications need not recite structure or formula or chemical name for nucleotide sequences of claimed chimeric genes where such sequences are known in the art).

The Examiner further questions how it is possible that "48 examples, as stated by appellants could be considered representative of what the appellant[s] consider to be 'a multitude of nucleic acids' encompassed in the claimed invention," and argues that the claims are overly broad because "[they] are not limited to the 9 species of wild-type . . . or the 39 species of mutant nucleic acid sequences" discussed in the Appeal Brief. (Ans. 16, 19.) We are not persuaded. Compliance with the written description requirement does not require each species of a claimed genus to be disclosed. Instead, what is required is "a representative number of species . . . or structural features common to the members of the genus" so as to allow a skilled artisan to "'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (citation omitted). The Examiner neither addresses the statements in Dr. McFadden's declaration regarding why the Anthozoan species disclosed in the Specification might be considered representative, nor explains why the disclosure in the Specification regarding conserved amino acids in the encoded polypeptides of the eight species does not suggest representativeness. (Spec. Fig. 23.)

The Examiner argues that the recited β-can fold with a chromophore and fluorophore also does not suffice as "a structural feature to describe specific embodiments of the claimed invention." (Ans. 17–18.) In particular, the Examiner argues that "there are no indicia in the instant specification of a specific structure possessing a β-can fold," that "a

structure including a [β]-can fold does not define the composition of the amino acids in said structure," and that "possession of a chromophore," likewise, "does not define the entire structure of a protein." (*Id.*)

We are not persuaded. Appellant has represented that "all of the exemplary amino acid sequences of the disclosed Anthozoan polypeptides contain a β-can fold," and this statement appears supported by the Specification. (Reply Br. 7–8; Spec. 29:30–32 ("In many embodiments, the subject homologues have structural features found in the above provided specific sequences, ***where such structural features include the β-can fold***.") (emphasis added).) Similarly, while different amino acid sequences can form a β-can fold, and a β-can fold secondary or tertiary structure thus may not have a one-to-one correspondence with the primary structure of a protein, the Specification has also provided multiple examples of non-bioluminescent Anthozoan proteins having a β-can fold, together with indications of amino acids that are conserved across these proteins and mutations that do not appear to affect the β-can fold structure. (*See, e.g.*, Spec. Figs. 1–9, 23, Tables 1, 2.)

With respect to the Examiner's argument that a chromophore does not define the entire structure of the protein, we note that to satisfy the written description requirement it is not necessary that the Specification discloses the entire structure of each species within a genus. Rather, as already discussed above, it is only necessary that there be disclosure of "structural features ***common to the members of the genus*** so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (citation omitted) (emphasis added).

We also note, but are not persuaded by, the Examiner's additional

arguments that the claim limitations regarding molecular weight, absorbance maximum, and emission maximum do not sufficiently disclose the claimed genus of nucleic acid constructs because none of these limitations, by itself, defines the structure of the encoded protein. (Ans. 16–17, 18, 19.) While the Examiner's arguments may be factually accurate, the written description requirement is met for the reasons discussed above.

Claims 104 and 105

Claims 104 recites a humanized nucleic acid encoding the non-bioluminescent Anthozoan chromo- or fluorescent polypeptide or mutant that is also described in claim 71, while claim 105, which depends from claim 104, recites additional narrowing limitations relating to 40% sequence identity with certain reference sequences.

As discussed above, the Examiner finds that "the claimed invention . . . directed to a humanized nucleic acid encoding a fluorescent polypeptide . . . is not adequately described." (Ans. 8.) The Examiner does not dispute Appellant's explanation that "the humanized element refers to changes made to the nucleic acid sequence to optimize the codons for expression of the protein in human cells" and acknowledges that "[t]he art appears to recognize humanized proteins." (*Id.* at 8, 25; *see also* Spec. 24:9–14.) However, the Examiner argues that "[a] skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acids and the encoding polypeptides based on the limitations found in claim 104" because understanding of the humanization process "does not provide the missing structural elements in the claim." (Ans. 25.)

In light of the above, the Examiner's rejection of claims 104 and 105 also appear to be based on the Examiner's finding that the claimed genus of

nucleic acid and/or amino acid sequences relating to the recited chromo- or fluorescent polypeptide or mutants is insufficiently described. We find the rejection lacking for the same reasons described above regarding claim 71.

Claims 106 and 107

Claim 106 and 107 claims nucleic acid primers of 15 to 100 nucleotides in length that hybridize under stringent conditions of 50°C and 0.1×SSC to a nucleic acid, or the complement or complement thereof, that encodes a polypeptide recited in claim 71. The Examiner argues that "the recitation of a nucleic acid primer of 15 to 100 nucleotides that hybridizes under stringent conditions to a nucleic acid or complement thereof without providing a reference structure lacks adequate written description." (Ans. 25.)

As noted with approval in *Enzo*, the USPTO's Written Description Examination Guidelines suggests that "genus claims to nucleic acids based on their hybridization properties . . . may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Enzo*, 323 F.3d at 967. In light of our finding that the encoding sequence of claim 71 is sufficiently described, we find that Appellants have the better argument as to these claims as well.[8]

[8] We note that claims 106 and 107 differ from the scenario described in *Enzo* in that the claims recite "stringent" hybridization conditions rather than "highly stringent" conditions. However, the Examiner has provided no argument or evidence that a skilled artisan would not expect primers that hybridize to target polynucleotides under stringent, rather than highly stringent, conditions, to be similar in sequence.

Accordingly, we reverse the Examiner's rejection of claims 71 and 104–107. Having found the nucleotide acid constructs of claim 71 to be described, we are also not persuaded by the Examiner's similar arguments with respect to claims 79, 81, 83, 85, and 88. (Ans. 19.) Likewise, we find that dependent claims 72, 80, 82, 84, 89–103, and 109–115, which recite narrowing limitations regarding 40% or 70% identity to specific reference sequences and/or specific mutations or types of mutations, are also described for at least the same reasons discussed above for claim 71. Finally, the Examiner made no additional specific arguments regarding claims 73–78, 86, and 87. We therefore also reverse the Examiner's rejection of those claims for lack of written description, for the reasons already discussed.

II.

Issue

The Examiner has rejected claims 71–74, 76–82, 88, 91, 93, 95, 97, 99, 103, 109–111, and 114 under 35 U.S.C. § 101 as directed to non-statutory subject matter.

The Examiner finds that "[t]he claimed invention encompasses a coding sequence that is naturally occurring," including for instance naturally occurring mutants. (Ans. 9.) While claim 71 recites a nucleic acid construct that also comprises a vector, the Examiner points out that the Specification defines a vector as "a replicon, such as plasmid, phage or cosmid, to which another DNA segment may be attached so as to bring about the replication of the attached segment." (*Id.* at 10 (internal quotation marks omitted).) The Examiner finds that the broadest reasonable interpretation of vector thus encompasses "a chromosome segment comprising a coding region." (*Id.*) As to claim 76, which recites a nucleic acid construct prepared by inserting a

coding sequence into a vector, the Examiner further finds the claim to be a product by process claim that does not alter the structure of the coding sequence. (*Id.* at 11–12.) Likewise, the Examiner finds that the Kozak sequence and multiple cloning sites recited respectively in, e.g., claims 81 and 79, to be naturally present in a coding sequence. (*Id.* at 12.) Accordingly, the Examiner finds:

> [T]he instant specification discloses that a new fluorescent protein was discovered by applicant[;] however, there is no indication in the specification as to how the claimed subject matter markedly differs from a wild-type fluorescent protein. Further, there is no distinction made between the fluorescent protein or mutant thereof claimed and the natural form[;] thus, the claim language is not patent eligible . . . .

(*Id.* at 13.)

Appellants contend that the rejected claims recite a continuous open reading frame coding sequence, which is not naturally occurring. (Appeal Br. 96–99.) With respect to claim 71 and dependent claims, Appellants further argue that, in any event, "the . . . claimed nucleic acid construct that comprises the continuous open reading frame coding sequence together with a vector would rise to the level of marked difference." (*Id.* at 101–104, 113.) With respect to claims 72, 80, 82, 103, 109–111, and 114, which recite certain reference sequences, Appellants argue that the additional limitations in the claims further narrow the claims so as to render them patent eligible. (*Id.* at 102–103, 106, 107–108, 112–116.) With respect to claims 73, 74, 76–82, 110, and 111, which further define the claimed vector and/or the nucleic acid construct, Appellants argue that the additional limitations "will inherently result in the nucleic acid construct having a different structure and sequence than any naturally occurring nucleic acids,

e.g., through inclusion of heterologous nucleic acid sequence from the vector." (*Id.* at 103, 105–108, 114–115.) With respect to claims 88, 91, 93, 95, 97, 99, 103, and 114, which recite additional limitations relating to a mutant polypeptide, Appellants contend that the claimed polypeptide "will have different structural characteristics than any naturally occurring nucleic acid, which rises to the level of marked difference." (*Id.* at 109–113, 116.)

The issue with respect to this rejection is whether the evidence of record supports the Examiner's conclusion that claims 71–74, 76–82, 88, 91, 93, 95, 97, 99, 103, 109–111, and 114 are directed to patent ineligible subject matter.

Analysis

We analyze this issue under the Supreme Court's controlling precedent, *Assoc. for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S.Ct. 2107 (2013); *see also Alice Corp. Pty. Ltd. v. CLS Bank Int'l.*, 124 S.Ct. 2347, 2355 (2014) (instructing to first consider whether the claims are directed to an ineligible concept and, if so, then consider whether the claims individually and as an ordered combination recite sufficiently more to transform the claimed invention into patent-eligible subject matter). In *Myriad*, the Supreme Court found that claims directed to isolated DNA encoding the BRCA1 polypeptide and certain fragments thereof, to be directed to patent ineligible subject matter. *Id.* at 2113, 2117–2119. In particular, the Court found that, unlike the *Chakrabarty* bacterium that was "new 'with markedly different characteristics from any found in nature'," "separating the gene from its surrounding genetic material is not an act of invention." *Id.* at 2117. However, the Court found that:

> cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments. . . . [C]reation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring. Petitioners concede that cDNA differs from natural DNA in that "the non-coding regions have been removed." They nevertheless argue that cDNA is not patent eligible because "[t]he nucleotide sequence of cDNA is dictated by nature, not by the lab technician." That may be so, but the lab technician unquestionably creates something new when cDNA is made. cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived. As a result, cDNA is not a "product of nature" and is patent eligible under § 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.

Id. at 2119.

Claims 71–74, 76–78, 109

Claim 71 claims a nucleic acid construct comprising a vector and a continuous open frame coding sequence that encodes the recited non-bioluminescent Anthozoan chromo- or fluorescent polypeptide or mutant. Claims 72–74, 76–78, and 109 all depend directly or indirectly from claim 71. Claim 72 and 109 include narrowing limitations requiring the polypeptide or mutant to have 40% or 70% sequence identity with certain identified sequences. Claims 73, 74, 77, and 78 further characterize the structure of the nucleic acid construct by requiring certain sequences or types of vectors. Claim 76 recites that the construct is prepared by inserting the coding sequence into the vector.

Appellants first contend that the recited "continuous open reading frame coding sequence" is not naturally occurring because, like the cDNA found to be patent eligible in *Myriad*, it retains the exons and excludes the

introns, if any, of the genomic locus from which the sequence is derived.

(Appeal Br. 96–99.)

We are not persuaded. As summarized in *Myriad*,

> [c]reation of proteins from DNA involves two principal steps, known as transcription and translation. In transcription, the bonds between DNA nucleotides separate, and the DNA helix unwinds into two single strands. A single strand is used as a template to create a complementary ribonucleic acid (RNA) strand. The nucleotides on the DNA strand pair naturally with their counterparts, with the exception that RNA uses the nucleotide base uracil (U) instead of thymine (T). Transcription results in a single strand RNA molecule, known as pre-RNA, whose nucleotides form an inverse image of the DNA strand from which it was created. Pre–RNA still contains nucleotides corresponding to both the exons and introns in the DNA molecule. The pre-RNA is then ***naturally*** "spliced" by the physical removal of the introns. The resulting product is a strand of RNA that contains nucleotides corresponding only to the exons from the original DNA strand. The exons-only strand is known as messenger RNA (mRNA), which creates amino acids through translation.

Myriad, 133 S.Ct. at 2111 (emphasis added). As further explained in *Myriad*,

> It is also possible to create DNA synthetically through processes similarly well known in the field of genetics. One such method begins with an mRNA molecule and uses the natural bonding properties of nucleotides to create a new, synthetic DNA molecule. The result is the inverse of the mRNA's inverse image of the original DNA, with one important distinction: Because the natural creation of mRNA involves splicing that removes introns, the synthetic DNA created from mRNA also contains only the exon sequences. This synthetic DNA created in the laboratory from mRNA is known as complementary DNA (cDNA).

Id. at 2112. In short, although both cDNA and mRNA contain only exons, mRNA exists in nature while cDNA does not.

Under the broadest reasonable construction, a continuous open

reading frame coding sequence includes mRNA coding sequences. Such a construction is supported by the Specification, which states that "[n]ormally mRNA species have contiguous exons, with the intervening introns, when present, being removed by nuclear RNA splicing, to create a continuous open reading frame encoding the protein." (Spec. 17:1–5.) Accordingly, contrary to Appellant's argument, limitations in the claims relating to a "continuous open reading frame" do not necessarily render the claims patent eligible.

Our findings regarding "continuous open reading frame" does not end our inquiry. Appellants next argue that, "even if the continuous open reading frame coding sequence was considered to be naturally occurring, the instantly claimed nucleic acid construct that comprises the continuous open reading frame coding sequence together with a vector would rise to the level of marked difference." (Appeal Br. 101.)

The Examiner contends that "[t]he broadest reasonable interpretation of [vector] is a chromosome segment comprising a coding region." (Ans. 10.) The Examiner further contends that "[i]f the natural gene is taken out of the organism and inserted into a vector, the gene remains the same," and that "[t]here is no evidence in the claim or instant specification that the gene is altered." (*Id.* at 12.)

Appellants respond that the Examiner's construction of vector as encompassing a chromosome is "plainly inconsistent with how the claim term would be interpreted by one of ordinary skill in the art in view of the specification":

> The specification is directed to the cloning and modification of Anthozoan chromo- and fluorescent protein encoding nucleic acids. The Specification provides specific examples where plasmid vectors

> are utilized for cloning and expression of coding sequences. There is no description in the specification of a construct comprising a chromosome and a continuous open reading frame coding sequence that are non-heterologous. In addition, the specification does not describe a naturally occurring continuous open reading frame coding sequence that encodes a chromo- or fluorescent Anthozoan polypeptide that includes the limitations as set forth in Claim 71.

(Reply Br. 14.) Appellants also contend that the dependent claims, which contain additional limitations with respect to the nucleic acid construct such as multiple cloning sites (MCS), would lead a skilled artisan to interpret *vector* as "not includ[ing] a chromosome that is non-heterologous to the continuous open reading frame coding sequence." (*Id.*)

We are not persuaded that Appellants' narrow construction of vector is correct in light of the broad and explicit definition of vector in the Specification. Nevertheless, we find that the Examiner has not shown the combination of a vector and the continuous open reading frame coding sequence recited in claim 71 to be a patent-ineligible natural phenomenon. We further explain our reasoning below.

The Specification defines a vector as "a replicon, such as plasmid, phage or cosmid, to which another DNA segment may be attached so as to bring about the replication of the attached segment." (Spec. 4:28–29.) Replicon is defined variously in dictionaries to be simply "a linear or circular section of DNA or RNA which replicates sequentially as a unit,"[9] "any genetic element that can regulate and effect its own replication from

[9] "replicon." *Merriam-Webster Online Dictionary*, https://www.merriam-webster.com/dictionary/replicon (last visited April 28, 2017).

initiation to completion,"[10] "[a] genetic element that undergoes replication as an autonomous unit,"[11] "[a] segment of a chromosome (or of the DNA of a chromosome or similar entity) that can replicate, with its own initiation and termination codons, independently of the chromosome in which it may be located," [12] and "[t]he replication unit; several are found per DNA in eukaryotic system."[13] The second portion of the Specification's definition of vector, i.e., that it permits "another DNA segment [to] be attached so as to bring about the replication of the attached segment," also contains no requirement that the DNA segment attached to be heterologous. While Appellants point to examples in the Specification where vectors comprise heterologous nucleic acid sequences, we do not import limitations from the Specification into the claims. *See, e.g., Bayer AG v. Biovail Corp.*, 279 F.3d 1340, 1348 (Fed. Cir. 2002). Accordingly, we do not find that a skilled artisan, in light of the Specification, would interpret a nucleic acid construct comprising a vector and coding sequence to exclude a chromosomal segment that is non-heterologous to the coding sequence.

Nevertheless, the definition of the vector in the Specification suggests that the nucleic acid construct of claim 71 should be interpreted to require the continuous open reading frame to be a DNA segment, rather than, e.g.,

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[10] "replicon." http://www.dictionary.com/browse/replicon?s=t (last visited April 28, 2017).
[11] "replicon." http://www.thefreedictionary.com/Replicon+(genetics) (last visited April 28, 2017).
[12] "replicon." http://medical-dictionary.thefreedictionary.com/Replicon+(genetics) (last visited April 28, 2017).
[13] *Id.*

an mRNA sequence, because a vector is defined as a replicon "to which ***another DNA*** segment may be attached so as to bring about the ***replication*** of the attached segment." (Spec. 4:28–29 (emphasis added).) We further agree with Appellants that a continuous open reading frame ***DNA*** coding sequences encoding the polypeptide recited in claim 71 does not fall within the judicial exception of natural phenomena, because they are similar to the cDNA sequences found to be patent eligible in *Myriad*. *Myriad*, 133 S.Ct. 2107 at 2119. We are not persuaded by the Examiner's argument that claim 71 does not recite a cDNA (Ans. 27–28), because, regardless of the wording used, the rationale the Supreme Court articulated in finding cDNA to be patent eligible also applies to a "continuous open reading frame" DNA sequence. We are likewise not persuaded by the Examiner's argument that "some genomic sequence can have a contiguous open reading frame and there is no exclusion of these structures in the claim language." (*Id*. at 28–29.) The Examiner has not provided any persuasive evidence or explanation suggesting that a genomic sequence ***coding for the polypeptide recited in the claims*** naturally have a continuous open reading frame, while Appellants have provided evidence that removal of introns is required to arrive at least one such "continuous open reading frame."[14] (Appeal Br. 97.)

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[14] The Examiner suggests that the Specification's description of certain nucleotide sequences as "wild type" or as "found in, derived from, or are mutants or homologues of nucleic acids found in *Anthozoan* organisms" indicate that such sequences occur in nature. (Ans. 9, 28.) We are not convinced. Derivation from a natural organism does not automatically result in lack of patent eligibility: cDNA, which the Supreme Court has held to be patent-eligible, may be said to be "derived from" a natural organism as well, as it is generally created from mRNA. *Myriad*, 133 S.Ct. at 2119. Likewise,

Given the above, we find that the Examiner has not established that it is more likely than not that claim 71 reads on a naturally occurring nucleic acid construct, or one that is not markedly different from a naturally occurring nucleic acid construct. Accordingly, we reverse the Examiner's rejection of claim 71 and dependent claims 72–74, 76–78, and 109.

Claims 79, 80, 110

Claim 79 recites a nucleic construct comprising (1) a continuous open reading frame coding sequence that encodes a nonbioluminescent Anthozoan chromo- or fluorescent polypeptide, or a chromo- or fluorescent mutant thereof, that has the characteristics of the polypeptide recited in claim 71 and (2) a multiple cloning site. Claims 80 and 110 depend from claim 79 and further requires that the nucleic acid of claim 79 has a 40% or 70% sequence identity with a sequence selected from specified sequences.

The Examiner contends that

> multiple cloning site . . . is found in the naturally occurring coding sequence as evidenced by the disclosure at paragraph [0189] which discloses that, "[B]oth wild type (wt) and mutant zFP538 DNA were amplified via PCR and reconstructed to EGFP-N1 backbone. This vector has the same multiple cloning sites as EGFP-N1. **Both pYNFPwt and pYNFPW129V keep the same multiple cloning sites** as EGFP-N1.["]

(Ans. 12 (emphasis added).) We are not persuaded. The portion of the Specification cited by the Examiner shows that the Anthozoan DNA was attached to a vector (i.e., the EGFP-N1 backbone) and that the resulting

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we agree with Appellants that "wild type" in this context does not indicate that the sequences necessarily occur in nature (Reply Br. 12–13), but rather simply means non-mutant.

vector retained the multiple cloning sites present on the original vector. This disclosure does not suggest that the Anthozoan DNA itself contains multiple cloning sites. Accordingly, we find that the Examiner has not established a prima facie case of patent ineligibility with respect to claim 79 and dependent claims 80 and 110 and reverse the Examiner's rejection of these claims.

Claims 81, 82, 111

Claim 81 recites a nucleic construct comprising (1) a continuous open reading frame coding sequence that encodes a nonbioluminescent Anthozoan chromo- or fluorescent polypeptide, or a chromo- or fluorescent mutant thereof, that has the characteristics of the polypeptide recited in claim 71 and (2) a Kozak sequence. Claims 82 and 111 depend from claim 81 and further requires that the nucleic acid of claim 81 has a 40% or 70% sequence identity with a sequence selected from specified sequences.

The Examiner contends that "it is well established in the art that a Kozak sequence or Sine-Dalgarno sequence is an initiation sequence that is naturally present in a coding sequence." (Ans. 12.) The Examiner also appears to argue, in the alternative, that the addition of a Kozak sequence "do[es] not add significantly more to the judicial exception" of the coding sequence. (*Id.* at 33.) Appellants contend that claim 81 "will inherently result in the nucleic acid construct having a different structure and sequence than any naturally occurring nucleic acids, e.g., through the inclusion of the heterologous nucleic acid sequence of the Kozak sequence together with the continuous open reading frame." (Appeal Br. 107.)

The Examiner has not cited evidence showing that the Kozak sequence is naturally present in a coding sequence encoding the recited

Anthozoan polypeptide or explained why its addition, to the extent it is not naturally present, would not render the resulting nucleic acid construct "markedly different" from a naturally occurring coding sequence. Because "the Examiner bears the initial burden . . . of presenting a prima facie case of unpatentability," *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992), we reverse the Examiner's rejection of claim 81 and dependent claims 82 and 111.

Claims 88, 91, 93, 95, 97, 99, 103, 114

Claim 88 recites a continuous open reading frame nucleic acid encoding chromo- or fluorescent ***mutant*** polypeptide of a non-bioluminescent Anthozoan chromo- or fluorescent polypeptide, having the characteristics of the polypeptide recited in claim 71. Claims 91, 93, 95, 97, 99, 103, and 114 all dependent from claim 88. Claims 91, 93, 95, and 97 further recites that mutant is a fluorescent protein from a particular species. Claims 103 and 114 further requires that the nucleic acid of claim 88 has a 40% or 70% sequence identity with a sequence selected from specified sequences.

Unlike claim 71, claim 88 does not require a nucleic acid construct comprising a vector. As discussed above, a continuous open reading frame nucleic acid encoding a wildtype non-bioluminescent Anthozoan chromo- or fluorescent polypeptide encompasses natural phenomena, because it encompasses mRNA sequences. Furthermore, none of the claims recited above exclude naturally occurring mutants. Given that natural mutations are well known (Spec. 6:17–19 (discussing "naturally-occurring mutational events"), we agree with the Examiner that claims 88, 91, 93, 95, 97, 99, 103,

and 114 encompasses patent-ineligible subject matter.[15]

Appellants cite as support the USPTO's 2014 Interim Guidance on Patent Subject Matter Eligibility ("Interim Guidance").[16] In particular, Appellants points to Claim 2 of Example 7 in the Interim Guidance's Nature-Based Product Examples—"Isolated nucleic acid comprising a sequence that has at least 90% identity to SEQ ID No. 1 and contains at least one substitution modification relative to SEQ ID No. 1"—which was found in the Interim Guidance to be patent eligible. We are not persuaded. As an initial matter, we are not bound by the Interim Guidance. Furthermore, we find the instant claims distinguishable from the example in the Interim Guidance, which requires a specific type of mutation (substitution) and specifies that "[n]o substitution modifications of [the gene at issue] are known to occur in nature."

Accordingly, we affirm the Examiner's rejection of claims 88, 91, 93, 95, 97, 99, 103, 114 as directed to patent-ineligible subject matter.

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[15] We note, but are not persuaded by, Appellants' arguments that claims 103 and 114 are further patent eligible because they contain additional narrowing limitations that "further ensures that the claim[s] . . . do[] not improperly tie up the future use of any alleged judicial exception encompasse[d] by the claimed nucleic acid construct." (Appeal Br. 112–113, 116.) While these claims are indeed narrower than claim 88, they are still more likely than not to encompass patent-ineligible subject matter (i.e., a naturally occurring mutant).

[16] *2014 Interim Guidance on Patent Subject Matter Eligibility*, 79 Fed. Reg. 74,618 (Dec. 16, 2014), available at https://www.federalregister.gov/articles/2014/12/16/2014-29414/2014-interim-guidance-on-patent-subject-matter-eligibility.

SUMMARY

We reverse the Examiner's rejection of claims 71–107 and 109–115 as lacking in written description.

We reverse the Examiner's rejection of claims 71–74, 76–82, and 109–111 as directed to patent ineligible subject matter.

We affirm the Examiner's rejection of claims 88, 91, 93, 95, 97, 99, 103, 114 as directed to patent ineligible subject matter.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART